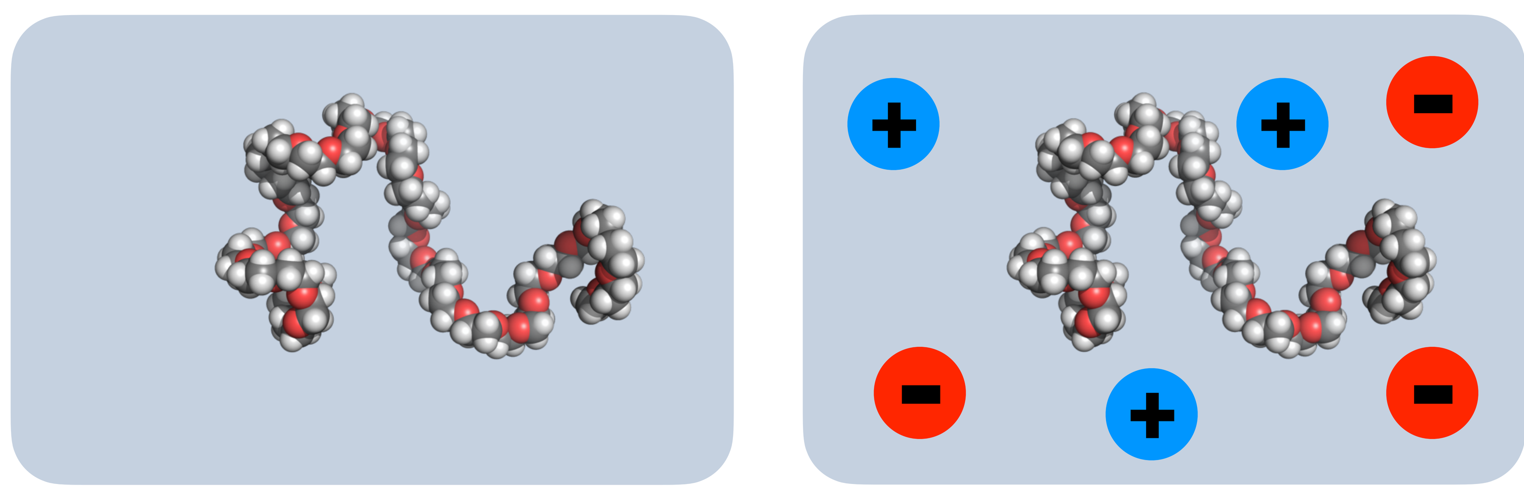
Step 1: Generation of ensembles of solute structures ψ

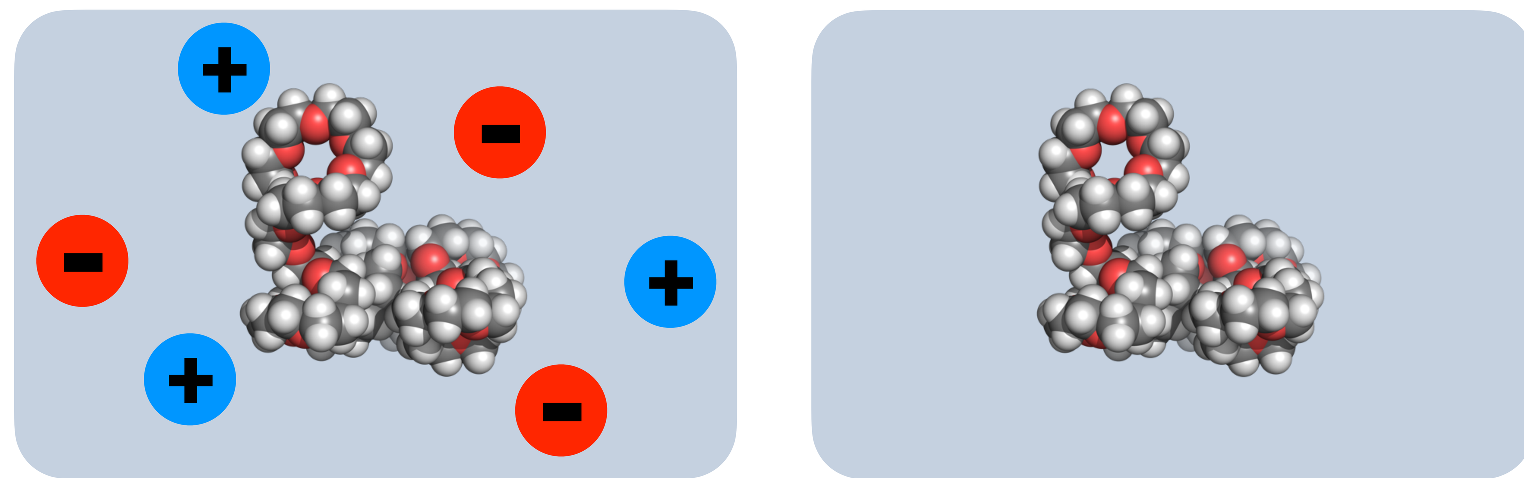
with $P_A(\psi)$ with $P_B(\psi)$

Step 2: Generation of solvent configurations in the presence of rigid solute and calculations of the solvation free energies



$\nu_A^{\mathrm{solv}}(\psi)$ $\nu_B^{\mathrm{solv}}(\psi)$

$$\Delta\nu^{\mathrm{solv}}(\psi) = \nu_B^{\mathrm{solv}}(\psi) - \nu_A^{\mathrm{solv}}(\psi)$$



$\nu_B^{\mathrm{solv}}(\psi)$ $\nu_A^{\mathrm{solv}}(\psi)$

$$\Delta\nu^{\mathrm{solv}}(\psi) = \nu_B^{\mathrm{solv}}(\psi) - \nu_A^{\mathrm{solv}}(\psi)$$

Step 3: Calculations of $\Delta\mu^{\mathrm{ex}}$ and its upper and lower bounds

$$\sum_{\psi_i \in A, i=1}^{N_A} F\left(\Delta\nu^{\mathrm{solv}}(\psi_i) - \Delta\mu^{\mathrm{ex}}\right) = \sum_{\psi_i \in B, i=1}^{N_B} F\left(-\Delta\nu^{\mathrm{solv}}(\psi) + \Delta\mu^{\mathrm{ex}}\right)$$

(equation for $N_A = N_B$)

$$\Delta\mu^{\mathrm{ex}}_{\mathrm{upper}} = \frac{1}{N_A}\sum_{\psi_i \in A, i=1}^{N_A} \Delta\nu^{\mathrm{solv}}(\psi_i)$$

$$\Delta\mu^{\mathrm{ex}}_{\mathrm{lower}} = \frac{1}{N_B}\sum_{\psi_i \in B, i=1}^{N_B} \Delta\nu^{\mathrm{solv}}(\psi_i)$$